57

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REVIEW

Prenatal and Postnatal Effects of Low-Level Lead Exposure: Integrated Summary of a Report to the U.S. Congress on Childhood Lead Poisoning[1]

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This article provides an integrated summary of a report to Congress from the Federal government (ATSDR) on childhood lead poisoning in the United States, with particular reference to low-level lead exposure and its effects on the fetus and the preschool child. As mandated by Section 118(f)(1)(C) of the 1986 Superfund Amendments and Reauthorization Act (SARA), ATSDR has examined the full spectrum of human *in utero* and postnatal lead toxicity, with emphasis on low-level neurotoxicity and adverse impacts on growth indices in risk populations. Especially important has been assessment of the relative persistence of these effects in later life as discernible from a number of longitudinal studies now under way around the world. Included in the Congressional report were discussions of dose–effect and dose–response relationships using blood lead levels as the indicator of lead dose.

INTRODUCTION

From a scientific and public health perspective, lead exposure and its toxic effects remain an important social issue in the United States. This persistence of an otherwise fully preventable health problem stems from a number of causes, including the extreme difficulty of effective lead exposure abatement and the development of a consensus among lead specialists that the scope of lead toxicity is much broader and more subtle than once recognized.

In taking note of this developing awareness that low-level lead toxicity is an important health problem, the U.S. Congress legislatively directed the Federal government to provide a comprehensive and quantitative examination of childhood lead intoxication in the United States (U.S. ATSDR, 1988). This assessment included (1) a full description of low-level lead intoxication in U.S. risk groups and

[1] A summary, with selective updating, of Chap. IV (Adverse Health Effects of Lead: Relationship to Public Health Risk and Societal Well Being) and portions of Chaps. II, III, and VIII, contained in *The Nature and Extent of Childhood Lead Poisoning in Children in the United States. A Report to Congress*, submitted July 1988 by the Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Public Health Service.

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the potential for persistence into later life, (2) a stratified estimation of numbers of lead-exposed subjects in the United States, and (3) estimation of numbers of young children exposed to lead in source-specific ways.

This paper presents an integrated summary of various chapters of the Congressional report that dealt with the characterization of low-level lead exposure and its adverse health effects. For historical purposes, the whole spectrum of adverse effects is also briefly presented. Of particular interest are prenatal and postnatal effects on the developing nervous system and effects on other indices of growth.

Various dose–effect and dose–response relationships for lead exposure and the relative persistence of effects into later life are also discussed.

A. THE EXPOSURE (DOSE) INDEX IN ASSESSMENT OF THE ADVERSE HEALTH EFFECTS OF LEAD IN HUMAN POPULATIONS

Assessing exposure of human populations to lead can be done either by environmental monitoring or by systemic, i.e., biological, monitoring. In the former case, lead is measured in environmental media serving as human exposure routes while in the latter, lead is measured in some biological medium directly or through some early biochemical change. A critical assessment of types of monitoring of toxic metal exposure has been published (Clarkson *et al.*, 1988). At present, biological monitoring is more commonly used in clinical and epidemiological studies of lead exposure and toxicity (Mushak, 1989; Skerfving, 1988; U.S. EPA, 1986).

At the present time, the concentration of lead in whole blood (μg Pb/dl whole blood, Pb–B) is the most commonly used and widely interpretable biological index of integrated or systemic lead exposure in human populations and arising from either acute or chronic exposure. Blood is readily accessible and relatively convenient to obtain by competent personnel. Most other body compartments and target organs/tissues are not as easily sampled (Mushak, 1989; Chap. 9, U.S. EPA, 1986; CDC, 1985; Piomelli *et al.*, 1984; Chisolm and Barltrop, 1979).

Blood lead levels are now understood to variably represent recent exposure (Mushak, 1989; Chaps. 9, 10, 11, U.S. EPA, 1986; Annest *et al.*, 1983; Chisolm and Barltrop, 1979) and some degree of more remote uptake of the toxicant. For example, experimental studies with adult volunteers (Rabinowitz *et al.*, 1976; Chamberlain, 1983) and epidemiological surveys of blood lead in the U.S. population which can be related to changes in exposure (Annest *et al.*, 1983) suggest that concurrent exposure is reflected in Pb–B over a period of 3–5 weeks.

In cases where subjects have increased body lead stores in mobilizable form, e.g., compartments of the skeleton, blood lead will be augmented by some fraction of endogenous, previously accumulated toxicant with much longer biological half-times. Evidence for this exists from follow-up studies of lead-exposed children (Otto *et al.*, 1985), from longitudinal studies of lead-exposed infants (Succop *et al.*, 1987), and from follow-up studies of retired lead workers (Skerfving, 1988; Christoffersson *et al.*, 1984) and other adults (Manton, 1985).

A strong advantage of Pb–B as indicator of lead dose is its traditional use in quantitation of dose–effect and dose–population response for lead. This is extremely important, since a biological indicator must not only link external to internal exposure, but also must connect internal dose with some adverse effect or

probability of some defined effect. At present, no other biological measure of lead, e.g., plasma lead, lead in urine or heme effect indicator can be so used (Clarkson *et al.*, 1988; Chaps. 9, 10, 11, U.S. EPA, 1986; CDC, 1985).

Despite its wide use as a lead exposure indicator, blood lead has a number of limitations. As implied above, this index reflects mainly recent exposure with an undefined input from past lead stores. For a key risk group, preschool children with variable lead exposure, serial Pb–B measurement may be required to ascertain early exposure, e.g., at 2 years of age, or a Pb–B measurement may need to be combined with other exposure indices. For example, it has been shown that blood lead may understate the potentially toxic fraction in the body, a fraction which is more quantitatively revealed by the provocative chelation or lead mobilization test (Mushak, 1989; Rosen *et al.*, 1989; Chap. 10, U.S. EPA, 1986; CDC, 1985; Piomelli *et al.*, 1984).

Furthermore, the value of maternal Pb–B at delivery in tandem with cord blood lead level is still inconclusive as a full measure of intrauterine exposure in perhaps the most vulnerable group, the developing fetus. Serial maternal Pb–B measurement in high-risk pregnancy groups might be better.

With regard to trends and directions, the continuous downward revision of lead exposure levels deemed to be "safe" places further demands on accurate and interpretable biological indices of exposure. If one is now to consider Pb–Bs in the range of 10–15 μg/dl as levels of concern, then measurement of Pb–B at or below these concentrations will be routinely required.

In addition, there would not appear to be meaningful early effect indicators now in routine use which could easily substitute for Pb–B in the region below 25 μg Pb/dl (CDC, 1985). The *in vivo* measurement of lead in long bone of preschool children and in pregnant women does offer much promise, although this approach is only now coming into use (Rosen *et al.*, 1989).

B. VARIOUS ADVERSE HEALTH EFFECTS OF LEAD IN CHILDREN

There is currently a vast scientific, clinical, and epidemiological database documenting the variety and the intensity of adverse effects of lead on different tissues and organ systems of young children and other high-risk segments of the general population.

Such adverse effects involve many levels of physiological and anatomical organization within the human body, ranging from the cellular/subcellular level and progressing to higher degrees of functional and structural organization. At a high enough level of lead exposure, i.e., >40 μg/dl, virtually all body systems will be injured or have a high risk of injury. The full spectrum of such adverse effects has been comprehensively examined in such reports as that of the EPA (U.S. EPA, 1986) and the National Research Council (NAS, 1980).

The report to Congress (U.S. ATSDR, 1988) placed primary emphasis on those effects which are likely to occur at relatively low or prevalent chronic levels of lead exposure in the United States and which can potentially affect several millions of children, as estimated in Chapter V of the Congressional report. As in the Congressional report, much of the attention in this article is given to neurotoxic effects of low-level lead exposure in the fetus and the young child, especially as

these are being revealed in longitudinal studies around the world. Lead-associated hematotoxicity and adverse impacts on growth and development indices are also described in some detail. Clinically manifest, serious cases of lead poisoning still occur, especially in major U.S. cities and this persisting health issue is acknowledged here and in the Congressional report.

1. Neurotoxic Effects of Lead in Young Children

Although lead has diverse health effects, its neurotoxic effects in children are particularly notable because of the sensitivity of the developing central nervous system (CNS) to lead exposure and the prevailing clinical view that lead-associated CNS injury is difficult to reverse. At present, the developing CNS is considered to be the principal target system for lead toxicity in children.

From a historical perspective, scientific and clinical perceptions of what constituted lead neurotoxicity have been drastically revised over the years and to the present. In the earlier part of this century, childhood lead neurotoxicity was primarily recognized as the result of acute, high-level lead exposure resulting, for example, from the ingestion of leaded paint chips (Chap. 12, U.S. EPA, 1986; CDC, 1985; NAS, 1972, 1980).

This most severe form of poisoning was often lethal. Prior to the introduction of chelation therapy, severe lead poisoning with encephalopathy had a mortality rate of 65% (NAS, 1972). Since the advent of chelation treatment, mortality rates have declined significantly. In the United States, the use and refinement of chelation therapy in lead poisoning owed much to the work of Chisolm and colleagues in Baltimore (NAS, 1972).

The Pb–B levels associated with such severe poisoning were quite high, >80 μg/dl, but were also quite variable, reflecting individual differences in vulnerability and varying times between the exposure episode, blood testing, and clinical intervention (U.S. EPA, 1986; NAS, 1972).

Children surviving acute poisoning episodes, with or without manifest encephalopathy, were often found to have severe neurological sequelae, traced to permanent damage to the central nervous system. Observations by Byers and Lord (1943) and later clinicians (see, e.g., Needleman *et al.*, 1974, and Perlstein and Attala, 1966) showed that children manifested mental retardation, seizures, optic atrophy, sensory-motor deficits, and behavioral dysfunctions long after their acute poisoning experiences. Perlstein and Attala (1966) reported such sequelae in 37% of children who suffered lead poisoning without evidence of encephalopathy.

Recent research in lead neurotoxicity has produced a progressive decline in the lowest exposure levels at which neurotoxic and other effects can be detected. Consequently, attention is now on effects of chronic, low-level lead exposure (although cases of severe poisoning still occur).

Epidemiologic studies have been the primary means of identifying the effects of prevalent lead exposure levels on populations of children. These studies have been of two general types: (1) cross-sectional or retrospective studies, and (2) longitudinal or prospective assessments.

Longitudinal or prospective designs have a number of advantages for the study of environmental pollutants. In the case of an accumulating toxicant such as lead,

prospective studies can more accurately match the effect-inducing lead exposure and the associated adverse effect than can the cross-sectional studies. This has now been shown to be especially true for prenatal and early postnatal neurotoxicity.

Therefore, important recent findings from a group of prospective studies are discussed first, followed by a summary of findings from cross-sectional and other investigations of childhood lead neurotoxicity.

a. Prospective studies of lead neurotoxicity. Findings from a group of well-conducted studies now indicate that disturbances in early neurobehavioral development occur at levels well below those considered "safe" or even "normal" in recent years. The most clearly identified effect thus far has been lower scores on the Mental Development Index of the Bayley Scales of Infant Development, a standardized test of infant intelligence. Other developmental endpoints, such as shorter gestational age and lower birth weight, have also been associated with prenatal lead exposure in many of these studies. These are discussed separately. Recent assessments of these studies have appeared (Grant and Davis, 1989; Davis and Svendsgaard, 1987).

To date, four prospective studies—those in Boston, Cincinnati, and Cleveland in the United States and in Port Pirie, Australia—have provided data which can be critically examined. In the aggregate, these studies have a quality of epidemiological design that yield evidence superior to that traditionally generated in single studies (Davis and Svendsgaard, 1987). The strengths of this cluster of studies include (1) employment of uniform, accepted, and sophisticated methodology for assessing exposure and outcome measures; (2) employment in all cases of appropriate statistical controls for many covariates and possible confounders; (3) use in all cases of study populations numbering in the hundreds, thereby offering greater statistical power to detect subtle effects; and (4) examination of the full scope of development, beginning with assessment of lead exposure *in utero*. By consistent use of the same outcome measures, these studies can be directly compared.

Table 1 summarizes some of the key features of the four prospective studies reviewed below. The Bayley Scales of Infant Development comprise three indexes of mental, motor, and emotional development. Of particular importance is the Mental Development Index (MDI), which was designed to assess "sensory–perceptual acuities, discriminations, and the ability to respond to these; the early acquisition of 'object constancy' and memory, learning, and problem-solving ability; vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking" (Bayley, 1969, p. 3). The scales have a mean of 100 and a standard deviation of 16.

The first prospective study to report effects of prenatal lead exposure on later postnatal development was conducted in Boston by Bellinger *et al.* (1984a). Blood lead levels were measured for 249 umbilical cords of infants born to middle- to upper-middle-class parents. The use of higher socioeconomic-status (SES) subjects complements the focus on lower SES subjects in most other lead studies. Multivariate regression analyses for 216 subjects showed an association between cord blood lead levels and performance on the Bayley MDI at 6 months of age.

TABLE 1
SUMMARY OF MAJOR FINDINGS FROM PROSPECTIVE STUDIES OF EARLY EXPOSURE TO LEAD[a]

Population average Pb–B (μg/dl)	Time of Pb–B measurement	Endpoint (deficit size)[b]	Population	Reference
14.0	Postnatal (6 months)	MDI[c] at 24 months (2 pts.)	Port Pirie, S. Australia	Vimpani *et al.* (1985, 1989)
20.6	Postnatal (24 months)	McCarthy Scales at 48 months (7.2 pts, 30 vs 10 μg/dl)	Port Pirie (continued)	McMichael *et al.* (1988)
15.8	Postnatal (48 months)			
6.5	Birth (cord)	MDI at 6, 12, 18, 24 months (4–8 pts)	Boston, MA	Bellinger *et al.* (1984a, 1985, 1986, 1987a)
6.8	Postnatal (24 months)	McCarthy Scales at 57 months (3 pts)	Boston (continued)	Bellinger *et al.* (1987b)
8.0	Prenatal (maternal)	MDI at 6, 12 months (8 pts)	Cincinnati, OH	Dietrich *et al.* (1986, 1987a, 1989)
5.8	Birth (cord)	MDI at 12 months via Neurological soft signs at birth	Cleveland, OH	Wolf *et al.* (1985) Ernhart *et al.* (1985a, 1986)

[a] Source: U.S. EPA, 1986, with partial updating.
[b] Deficit per 10 μg/dl increment in Pb–B, except for early Boston data and 4-year-old group in Port Pirie study; amount of deficit not stated in Cleveland study.
[c] MDI, Mental Development Index.

The covariate-adjusted difference between low (x = 1.8 μg/dl) and high (x = 14.6 μg/dl) lead exposure groups was nearly 6 points on the MDI. Continued follow-up of these subjects has shown that a 4- to 8-point deficit in MDI scores persisted at 12, 18, and 24 months of age (Bellinger *et al.*, 1985, 1986, 1987a). No effect was evident using postnatal blood lead levels.

More recently, Bellinger *et al.* (1987b) have reported that the Boston cohort of children also show cognitive deficits on the McCarthy Scales of Children's Abilities at about 5 years of age. Although initial analyses do not indicate that these deficits can be attributed to prenatal lead exposure (after adjusting for the influence of potentially confounding factors), they do show a significant relationship to earlier blood lead levels (at 24 months) rather than concurrent levels.

Dietrich *et al.* (1986, 1987a, 1989) enrolled 305 pregnant women from the inner city of Cincinnati and measured their blood lead levels at the first prenatal clinic visit (x = 8.0 μg/dl for 245 subjects). Blood lead concentrations of the newborn infants were determined at Postnatal Day 10 (x = 4.5 μg/dl for 280 subjects).

Regression analyses (including a statistical technique known as structural equation modeling) indicated that prenatal lead exposure was inversely related to male infants' scores on the 6-month Bayley MDI as well as the Psychomotor Development Index (PDI).

The effects were both direct and indirect; that is, prenatal lead levels were not only directly related to impaired performance on the Bayley Scales, but were also related to reduced gestational age and reduced birth weight, which in turn were associated with lower MDI and PDI scores. The total direct and indirect effects of prenatal lead exposure on MDI scores amounted to approximately an 8-point deficit for every 10 μg/dl increase in blood lead level (Dietrich *et al.*, 1989). A

similar association was found between MDI scores and neonatal blood lead, but preliminary analyses using postnatal blood lead measurements at 3 and 6 months indicated no significant relationships (Dietrich *et al.*, 1989).

Thus, as in the Boston study, prenatal rather than postnatal lead exposure had the predominant influence on postnatal neurobehavioral performance. Interestingly, however, these effects were confined to the males in the Cincinnati study. It is important to note that the statistical significance and the magnitude of the effects described here were already adjusted for various factors such as maternal alcohol and tobacco usage, home environment, and SES. More recent analyses of 12-month data for this same cohort have indicated that deficits in the MDI and other effects persist at least through the first year of life (Dietrich *et al.*, 1987b), which, again, is consistent with findings from the Boston study.

Reports from Ernhart *et al.* (1985a, 1986, 1987) have also addressed the issue of prenatal lead exposure and postnatal neurobehavioral function as examined in a prospective study in Cleveland, Ohio. Maternal and cord blood samples were obtained at the time of delivery from 185 mothers (x = 6.5 μg/dl) and 162 infants (x = 5.8 μg/dl). Of these, only 132 samples were actual mother–infant pairs. The infants were evaluated on the Brazelton and Graham–Rosenblith neonatal behavioral assessment scales, which showed three significant effects (out of 17 outcomes examined) related to blood lead: abnormal reflexes, neurological soft signs, and muscle tonus.

Using the restricted data set of 132 mother–infant pairs, only neurological soft signs were significantly related to cord blood lead. A brief report (Wolf *et al.*, 1985) on later outcomes in this same cohort mentioned a statistically significant relationship between the neurological soft signs measure and the Bayley MDI scores at 12 months. Thus, despite the comparatively small number of subjects in this study, it appears, as noted by Davis and Svendsgaard (1987), that neurobehavioral effects of quite low prenatal lead exposure were detected at birth and that, indirectly, 12-month Bayley MDI scores may have declined as a result.

Another major prospective study is under way in Port Pirie, South Australia. Results of testing 592 children on the Bayley MDI and PDI scales at 24 months of age have been reported by Vimpani *et al.* (1985) and Baghurst *et al.* (1987). Multiple regression analyses indicated that lead exposure was significantly related to reduced MDI scores. For every 10 μg/dl increase in blood lead, scores on the 24-month MDI dropped an average of about 2 points, which is notably consistent with findings from the Boston and Cincinnati studies. However, unlike the latter studies, the strongest relationship in Port Pirie was found using postnatal blood lead.

Blood lead levels rose sharply in the Port Pirie cohort from about 14 μg/dl at 6 months of age to approximately 21 μg/dl at 15 months. Davis and Svendsgaard (1987) suggest that earlier testing on the Bayley Scales (e.g., at 6 months) might have revealed a stronger effect of prenatal exposure than could be detected later, after blood lead levels had increased so much between 6 and 15 months.

More recent analyses incorporating controls for maternal intelligence and quality of the home environment indicated that the blood lead–MDI relationship was

"markedly attenuated" when home environment measures were included in the multivariate regressions (Vimpani *et al.*, 1989). Nevertheless, the association between 6-month blood lead levels and 24-month MDI scores remained marginally significant ($P = 0.07$, Wigg *et al.*, 1988).

In their most recent report in the series, McMichael *et al.* (1988) examined lead exposure indexed in the time intervals noted, annual Pb–B analyses up to 4 years of age, and integrated postnatal average Pb–B level, in relationship to the McCarthy Scales of Children's Abilities at 4 years of age. Pb–B levels at each age, especially the 2- and 3-year levels, as well as the integrated level, were inversely correlated to development at age 4. Subjects with an average Pb–B of 30 μg/dl had a general cognitive score 7.2 points lower (95% CI, 0.3 to 13.2; mean 107.1) than children with an average Pb–B of 10 μg/dl. Perceptual–performance and memory scores were also affected. Notably, there were no evident thresholds for any of these effects.

Other prospective studies are being conducted by McBride *et al.* (1987) in Sydney, Australia, by Rothenberg *et al.* (1989) in Mexico City, Mexico, by Graziano *et al.* (1989) in Titova Mitrovica, Yugoslavia, and by Moore *et al.* (1989) in Glasgow, Scotland. The results from these studies are still in preliminary form or have not yet been reported in sufficient detail to allow critical evaluation.

In sum, the studies for which adequate information is available are remarkably consistent in identifying a link between low-level lead exposure during early development and later neurobehavioral performance as reflected in deficits on the Bayley Mental Development Index. Moreover, the studies generally point to the prenatal period of exposure as the most critical, although postnatal exposure may still be important and even overrride the effect of prenatal exposure under some conditions (McMichael *et al.*, 1988; Bellinger *et al.*, 1987b). Blood lead levels of 10 to 15 μg/dl, and possibly lower, constitute a level of concern for these effects (Davis and Svendsgaard, 1987; U.S. EPA, 1986).

The public health implications of a 2- to 8-point decline in Bayley MDI scores have been examined by Davis and Svendsgaard (1987) and Grant and Davis (1989). They noted that, although a change of a few points in the MDI for an individual child may not be clinically significant, a 4-point downward shift in a normal distribution of MDI scores for a population of children would result in 50% more children scoring below 80. This is statistically analogous to the observations and arguments of Needleman *et al.* (1982) for IQ scores in older children.

b. Cross-sectional and other studies of lead neurotoxicity. A great deal of important and useful information on the neurotoxic effects of lead in children has been provided by other epidemiological studies. A detailed and comprehensive evaluation of this body of work may be found in U.S. EPA (1986). Starting in the early 1970s, several studies were devoted to assessing the relationship between variables such as IQ and blood lead levels in various populations of children with known exposure to lead (e.g., residents of smelter communities or inner-city children identified through lead screening programs). Comparatively, exposure levels for these subjects were quite high, with mean levels well above 50 μg/dl in many instances.

De la Burde and Choate (1972) found various neurobehavioral dysfunctions and

IQ deficits in children whose Pb–B levels averaged 58 μg/dl at the time of assessment. Follow-up (de la Burde and Choate, 1975) indicated that the dysfunctions and deficits persisted. A variety of similar neurobehavioral impairments were also evident in both postencephalopathic children (Rummo, 1974; Rummo *et al.*, 1979) and "asymptomatic" children (Kotok *et al.*, 1977).

The difficulties in drawing conclusions about the likelihood of causal relationships from these early studies are illustrated by the work of Perino and Ernhart (1974), who found an association between lower IQ scores and Pb–B levels in children identified through the New York City lead screening program.

Follow-up investigation of these children, with control for parental education, led Ernhart *et al.* (1981) to conclude that the effect they had first reported was probably not due to lead or represented at best only a minimal effect on intelligence. Furthermore, after reanalysis of their earlier data, Ernhart *et al.* (1985b) concluded that their results provided no indication of an effect of lead on intelligence in these children. However, the reanalysis was done on 17 fewer children, from 80 down to 63, and reduced statistical power may be a factor.

Despite the limitations of the early epidemiologic investigations, their findings pointed the way for later studies at lower exposure levels. An important pioneering study of a general population of children without known elevated lead exposure was conducted by Needleman *et al.* (1979). The deciduous teeth of subjects were analyzed for lead content, which served as an indicator of cumulative lead exposure for the more than 2000 children enrolled in the study.

On the basis of classroom teacher ratings of the behavior of these children, an apparent dose–response relationship was found. More detailed analyses, taking into account various confounding variables, showed significant differences in IQ and certain other neurobehavioral measures for 58 high-lead children versus 100 low-lead children. Later analyses of the data from this study extended the findings and their implications. For example, Needleman *et al.* (1982) noted that a difference of 4 points in mean verbal IQs for the high- and low-lead groups meant that children in the high-lead group were 3.8 times as likely to have a verbal IQ below 80, and no high-lead children scored in the superior IQ range (>125). Follow-up investigation of the same children's school performance indicated that, 4 years later, high-lead children were significantly more likely to have been retained in grade (Bellinger *et al.*, 1984b).

Smith *et al.* (1983) investigated the relationship between lead levels in teeth and measures of behavior and intelligence in over 400 British children. These workers found that, after correcting for social class, home quality, and other confounding factors, the association between lead and IQ or academic performance was not statistically significant. Tooth-lead levels in these children were significantly below those reported in other industrialized countries. Reanalysis of these data by Pocock *et al.* (1989) did show an IQ effect in male subjects.

Similar findings were reported by Harvey *et al.* (1984) for almost 200 British children with low Pb–B levels (mean: 15.5 μg/dl). After adjusting for confounding variables such as social class in a subset (N = 48) of subjects, the association between blood lead and IQ was no longer significant. Social class may have also confounded the positive results of Yule and his colleagues in their studies of

British children. In their first study, IQ was reduced as a function of increasing blood lead level (Yule *et al.*, 1981), but a better controlled replication study (Lansdown *et al.*, 1986) showed no significant effect of lead on IQ. Other work by Yule and Lansdown (1983) and Hunter *et al.* (1985) showed no significant effect on IQ but did show significant effects on reaction time, consistent with findings by Needleman *et al.* (1979). Similarly, teacher ratings of high-lead children (Pb–B levels: 12 to 26 μg/dl) indicated behavioral impairments in line with the earlier findings of Needleman *et al.* (1979).

A series of studies in Germany by Winneke *et al.* (1982, 1983, 1984) parallel the British findings in several respects. Social variables appeared to play an important role in the associations between neurobehavioral function and lead exposure. With mean blood lead levels below 15 μg/dl, IQ scores were not significantly reduced, but reaction time performance and certain other neurobehavioral functions did show significant impairments (Winneke *et al.*, 1984).

Although the British and German studies show few if any significant associations between low-level lead exposure and cognitive function after controlling for social class, the findings are consistent in the direction of their effect and compatible with an overall dose–response relationship, with these studies falling at the low end of the lead–IQ relationship (U.S. EPA, 1986).

It may be, as Pocock *et al.* (1987) have concluded, that lead has little or no effect on IQ as measured in the British studies. But it is also quite possible that IQ tests or other aspects of the design and analysis of these studies are inadequate to detect lead-induced neurological impairments at the relatively low exposure levels involved (Smith, 1985).

Other recent studies provide more suggestive evidence that lead exposure at such relatively low levels may in fact be significantly associated with deficits in IQ. For example, Schroeder and Hawk (1987), in replicating earlier work (Schroeder *et al.*, 1985), found a highly significant linear relationship between IQ and blood lead level over a range of 6 to 47 μg/dl in a group of 75 black children. Since these children were all of low socioeconomic status, SES was not a confounder in this study. Studies by Fulton *et al.* (1987) in Edinburgh, Scotland, and by Hatzakis *et al.* (1987) in Lavrion, Greece, also provide strong evidence of IQ deficits related to children's lead exposure at blood lead levels below 25 μg/dl.

The cross-sectional linkage of lead exposure with child IQ and related neurobehavioral measures has also been noted in a Danish cohort (Hansen *et al.*, 1989), in an area of Europe, Scandinavia, not assumed to be heavily impacted by lead contamination. However, a cumulative index, lead in circumpulpal dentine, was used in lieu of Pb–B. When controlling for likely confounding variables, dentine lead was significantly correlated with Bender Visual Motor Gestalt Test, Verbal WISC, and Full Scale WISC. Notably, the results show a clear effect of lead across all socioeconomic groups. The "high" dentine group had Pb levels >18.7 ppm; the "low" group had values of <5 ppm.

Considered singly, none of the above studies can provide definitive evidence that low-level lead exposure is linked to reduced cognitive performance in children. However, Needleman (1987) recently reported the results of a metaanalysis of 13 such studies and noted that the joint probability of obtaining the reported

results was less than 3 in a trillion. Thus, the overall pattern of findings supports the conclusion that low-level lead exposure is related to neurobehavioral dysfunction in children.

In addition to the above assessments of the relationship of lead to cognition and behavior, other aspects of lead-associated neurotoxicity have been examined. Burchfiel *et al.* (1980) examined components of the EEG profiles for a subset of children studied by Needleman *et al.* (1979) and found significant differences in EEG activity in the higher dentine–lead group.

Otto and his co-workers (Otto *et al.*, 1981, 1982, 1985; Benignus *et al.*, 1981) have also evaluated neurophysiological function in relation to blood lead levels in children. Using various test paradigms, they have found disturbances in features of the EEG that correlate with Pb–B levels. In some cases, these effects appeared to persist for 2 to 5 years.

These investigators have also reported electrophysiological alterations measured through auditory brainstem evoked potentials (e.g., Robinson *et al.*, 1985, 1987). In addition, evidence of lead-related reduced hearing acuity has been reported by Robinson *et al.* (1985), supported by an analysis of audiometric data from the Second National Health and Nutrition Examination Survey (NHANES II) for children aged 4 to 19 years (Schwartz and Otto, 1987). The relationship between Pb–B level and hearing threshold was highly significant ($P < 0.0001$) for the large dataset from NHANES II. As noted by the authors, such impairment of hearing could contribute to other reports of neurobehavioral deficits such as learning disabilities and poor classroom behavior.

2. Adverse Effects of Lead on Child Growth and Development

Even a cursory review of the myriad effects of lead on children is beyond the scope of this report. However, certain recent findings related to child growth and development are summarized here because of their statistical and public health significance.

In addition to neurobehavioral endpoints, the prospective studies described above have examined various outcomes related to fetal and postnatal growth and maturation. In the Port Pirie study, McMichael *et al.* (1986) enrolled 831 pregnant women and followed 774 of the pregnancies to completion. Multivariate analysis showed that preterm deliveries (before the 37th week of pregnancy) were significantly related to maternal blood lead at delivery. If late fetal deaths were excluded, the association was even stronger: the relative risk of preterm delivery at exposure levels of 14 μg/dl or greater was 8.7 times the risk at levels up to 8 μg/dl.

The Cincinnati prospective study has also noted an effect of prenatal lead exposure on the duration of gestation. As mentioned above, Dietrich *et al.* (1986, 1987a, 1989) found that declines in Bayley scores were mediated in part by reduced gestational age associated with lead exposure. The effect amounted to about a half-week's reduction in gestation for about every 10 μg/dl increment in blood lead. Note that this effect was detected despite the fact that infants of less than 35 weeks gestational age were excluded from the Cincinnati study. Similarly, the Boston study (Bellinger *et al.*, 1984a) excluded infants of less than 34 weeks gestational age. As noted by Davis and Svendsgaard (1987) in their review of these

findings, such criteria would make it more difficult to detect an effect on duration of gestation.

Gestational age was also shown to be significantly reduced as a function of increasing cord or maternal blood lead levels in a well-conducted cross-sectional study of 236 mothers and their infants in Glasgow, Scotland (Moore *et al.*, 1982). The geometric mean blood lead level for the mothers was approximately 14 μg/dl and for the infants was approximately 12 μg/dl.

The clearest evidence concerning an effect of lead on birth weight and growth comes from the Cincinnati study. Preliminary analyses by Bornschein *et al.* (1987, 1989) have indicated that, for approximately every 10 μg/dl increment in blood lead, the decrease in birth weight ranged from 58 to 601 g, depending on the age of the mother. Birth length also appeared to be significantly related to maternal blood lead (−2.5 cm per log unit blood lead), although the effect was evident only in white infants.

Other prospective studies are suggestive but less definitive regarding birth weight and fetal growth. Bellinger *et al.* (1984a) reported data showing an exposure-related trend in the percentage of small-for-gestational-age infants in the Boston study, but the difference fell just short of statistical significance at $P = 0.05$. In Port Pirie, the proportion of low-birth-weight deliveries was more than double that outside Port Pirie (respective maternal blood lead levels: 10.4 vs 5.5 μg/dl). Yet within both groups, low-birth-weight pregnancies were (nonsignificantly) associated with *lower* blood lead levels. Also, regression analyses indicated no evidence of intrauterine growth retardation using "small-for-dates" data. To complicate matters further, head circumference was significantly inversely related to maternal blood lead, but crown–heel length showed no association with lead exposure.

Other findings from the Port Pirie study are pertinent here. Of the 23 miscarriages in this study, all but 1 occurred in the more highly exposed Port Pirie mothers. Also, 10 of 11 stillbirths occurred to Port Pirie women. Specifically, the proportion of stillbirths was 17.5/1000 live births in Port Pirie versus 5.8/1000 outside Port Pirie and 8.0/1000 for all of South Australia. Nevertheless, the average maternal blood lead level at delivery was significantly *lower* for stillbirths (7.9 μg/dl) than for live births (10.4 μg/dl). As noted by Davis and Svendsgaard (1987), these anomalous findings for birth weight and stillbirths in the Port Pirie study suggest the possibility that the fetus and/or placenta was acting as a "sink" for the mother's body burden in such cases.

Congenital malformations were also considered in the Port Pirie study, but no significant relationship to lead exposure was found. Unfortunately, too little information was presented on this aspect of the Port Pirie study by McMichael *et al.* (1986) to judge the strength of their conclusions. Although Ernhart *et al.* (1986, 1989) also reported no significant relationship between lead exposure and congenital malformations for the Cleveland study, that study had a comparatively small number of subjects and a limited range of blood lead values, which would have made it difficult to detect an effect of lead if one existed.

However, a retrospective study by Needleman *et al.* (1984) did report an association between cord blood lead and the occurrence of minor malformations in

4354 infants born in Boston. The effect was significant only for minor malformations (e.g., hemangiomas/lymphangiomas, hydroceles, skin tags, papillae, undescended testicles) taken as a whole, not for any single malformation. Also, unexpected significant reductions in first trimester bleeding, premature labor, and neonatal respiratory distress were found to be associated with higher prenatal lead exposure.

Although no definitive judgment can be reached at this point regarding the possible teratogenic effects of low-level lead exposure as far as congenital malformations are concerned, other effects of lead on fetal development seem more clearcut. As concluded by Davis and Svendsgaard (1987), the weight of available evidence suggests that the duration of gestation is affected by exposure to lead during pregnancy and that such effects can occur at blood lead levels below 15 μg/dl. In addition, birth weight and possibly other aspects of fetal growth appear to be reduced by prenatal lead exposure levels of less than 15 μg/dl. Recent analyses also suggest that delays in developmental milestones (e.g., age of first sitting up, walking, or speaking) are related to Pb–B levels in children (Schwartz and Otto, 1987).

Later growth also appears to be affected by lead exposure postnatally. Schwartz *et al.* (1986) have recently reported that an analysis of the NHANES II dataset revealed significant relationships between Pb–B levels and height ($P < 0.0001$), weight ($P < 0.001$), and chest circumference ($P < 0.026$) in young children (<7 years old). These growth milestones were inversely related to Pb–B levels over the range of 5 to 35 μg/dl. Work in Belgium by Lauwers *et al.* (1986) also points to a relationship between children's lead exposure and disturbances in physical growth up to about 8 years of age.

Although a number of potentially confounding variables were considered in these studies, a more definitive epidemiologic design would be a prospective study. Preliminary analyses of data for 260 infants from the Cincinnati prospective lead study (Shukla *et al.*, 1987) in fact indicate that covariate-adjusted growth rates are significantly related to postnatal increases in blood lead levels. This relationship was only evident in infants whose mothers had Pb–B levels of 8 μg/dl or higher.

3. Effects of Lead on Heme Biosynthesis, Erythrocyte Physiology, and Function and Erythropoietic Pyrimidine Metabolism

Effects of lead on the blood's biochemical functions are interrelated and have variable biological impact (Chap. 12, U.S. EPA, 1986; CDC, 1985; Piomelli, 1981; NAS, 1980; Moore *et al.*, 1980; Granick *et al.*, 1978). Heme, the iron-containing prosthetic or cofactor group in various organ heme proteins, is variably affected by lead. Organs in which heme is affected include the blood-forming tissue and the liver, kidney, and brain (U.S. EPA, 1986; Piomelli, 1981; Granick *et al.*, 1978). In addition to the direct effects of lead on heme biosynthesis, there are potentially significant indirect impacts on the central nervous system, caused by the lead-induced accumulation of δ-aminolevulinate (ALA), a potential neurotoxicant (discussed at length in U.S. EPA, 1986).

Figure 1 depicts graphically the various steps in the heme biosynthetic pathway

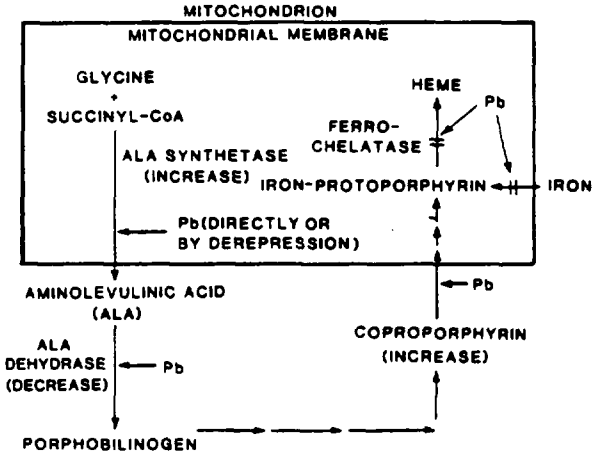

FIG. 1. Effects of lead on heme biosynthesis. Source: U.S. EPA (1986).

that are known to be affected by lead, although the actual mechanisms may not be fully understood in all cases. These steps include the feedback derepression (stimulation) of ALA-synthetase activity (Meredith *et al.*, 1978), the inhibition of ALA-dehydratase (porphobilinogen synthetase) activity (Hernberg and Nikkanen, 1970), coproporphyrin utilization (Piomelli and Graziano, 1980; Haeger-Aronsen, 1960), and the insertion of iron into protoporphyrin IX to form the prosthetic group, heme (Granick *et al.*, 1978). Companion effects on the uroporphyrins, which are mainly affected at relatively high exposure levels in humans, are also present (see, e.g., Piper and Tephly, 1974).

The accumulation of protoporphyrin IX (zinc protoporphyrin, ZPP; protoporphyrin in erythrocytes, EP) is not only an indicator of diminished heme biosynthesis, but also signals general mitochondrial injury, since the final step in heme biosynthesis, which includes EP, occurs in the mitochondria (Piomelli *et al.*, 1982; McKay *et al.*, 1969). Such subcellular injury may impair a variety of processes, including cellular energesis and calcium homeostasis. The various effects of lead within the heme biosynthesis pathway are shown qualitatively in Table 2. Quantitative relationships are given in the section on dose–effect relationships below.

Figure 2 graphically depicts lead-associated disturbances of the body heme pool. Most effects are documented, while some are only suggested by available experimental data. All of these effects can be summarized as follows:

(1) Hemoglobin effects—Lead can disturb the biosynthesis of hemoglobin, the general oxygen transport substance in mammals, leading in a dose-dependent manner to anemia and potential exacerbation of hypoxic responses to other toxic agents.

(2) Neural effects—Lead can reduce the amount of nervous system hemoproteins available for brain cellular energesis and development in neurons, axons, and glia.

(3) Renal and endocrine effects—Lead can disturb heme-mediated generation

TABLE 2
EFFECTS OF LEAD ON THE HEME BIOSYNTHESIS PATHWAY IN HUMANS

Step affected	Results	Comments
Inhibition of ALA-D activity	Accumulation of ALA in the body and excretion.	Plasma and urine levels rise; ALA itself may be neurotoxic at higher levels.
Feedback derepression of activity of ALA-synthetase	Accumulation of ALA in the body and excretion.	Much less sensitive than ALA-D activity; occurs at Pb-B > 40 μg/dl.
Inhibited conversion of coproporphyrin	Accumulation of coproporphyrin in urine.	Inhibition of coproporphyrin utilization; indicates ongoing lead exposure.
Inhibited conversion of protoporphyrin IX (EP) to heme	Accumulation of EP in red blood cells.	Sensitive measure of lead toxicity; elevation indicates mitochondrial injury.

of the important hormonal metabolite of vitamin D, 1,25-$(OH)_2$-vitamin D. This hormone serves a number of metabolic functions in humans, including regulation of calcium metabolism and function.

(4) Hepatic effects—Lead can impair the ability of heme-dependent liver enzyme systems to adequately detoxify foreign substances.

In addition to its effects on heme biosynthesis, lead has related effects on the cellular health and function of the red blood cell, inducing deleterious changes such as enhanced fragility and higher rates of lysis (U.S. EPA, 1986; NAS, 1980; Waldron, 1966). Such cell destruction can result in enough hemolytic loss of hemoglobin to significantly augment the lead-induced anemia that occurs through other routes. Lead-induced disturbances in red blood cell formation and maturation also occur by way of alterations in pyrimidine metabolism. Inhibition of the enzyme pyrimidine-5'-nucleotidase (Py-5'-N) impairs the degradation of large nucleic acid biomolecules and interferes with normal cellular energetics involved in the formation of the mature erythrocyte (Pagli and Valentine, 1975; Angle and McIntire, 1978).

C. DOSE–EFFECT/DOSE–RESPONSE RELATIONSHIPS FOR PEDIATRIC LEAD EXPOSURE

In this section, information from the two previous subsections is integrated to give a quantitative picture of the relationship between adverse outcomes and Pb–B levels in children. Outcomes are measured as either categorical variables or continuous variables, conventionally termed responses and effects, respectively. Thus, one may refer to either dose–response or dose–effect relationships, depending on whether the outcome is discrete or continuous.

Table 3 summarizes lowest observed effect levels (LOELs) for a variety of important adverse health effects in children, based on a critical evaluation and interpretation of these findings in U.S. EPA (1986), with updating. As shown in the table, the severity of effects increases as lead exposure levels increase. However, a constellation of effects, including alterations in neurobehavioral development and electrophysiological function, disturbances in heme biosynthesis, and deficits in growth and maturation, both prenatally and later in childhood, is evi-

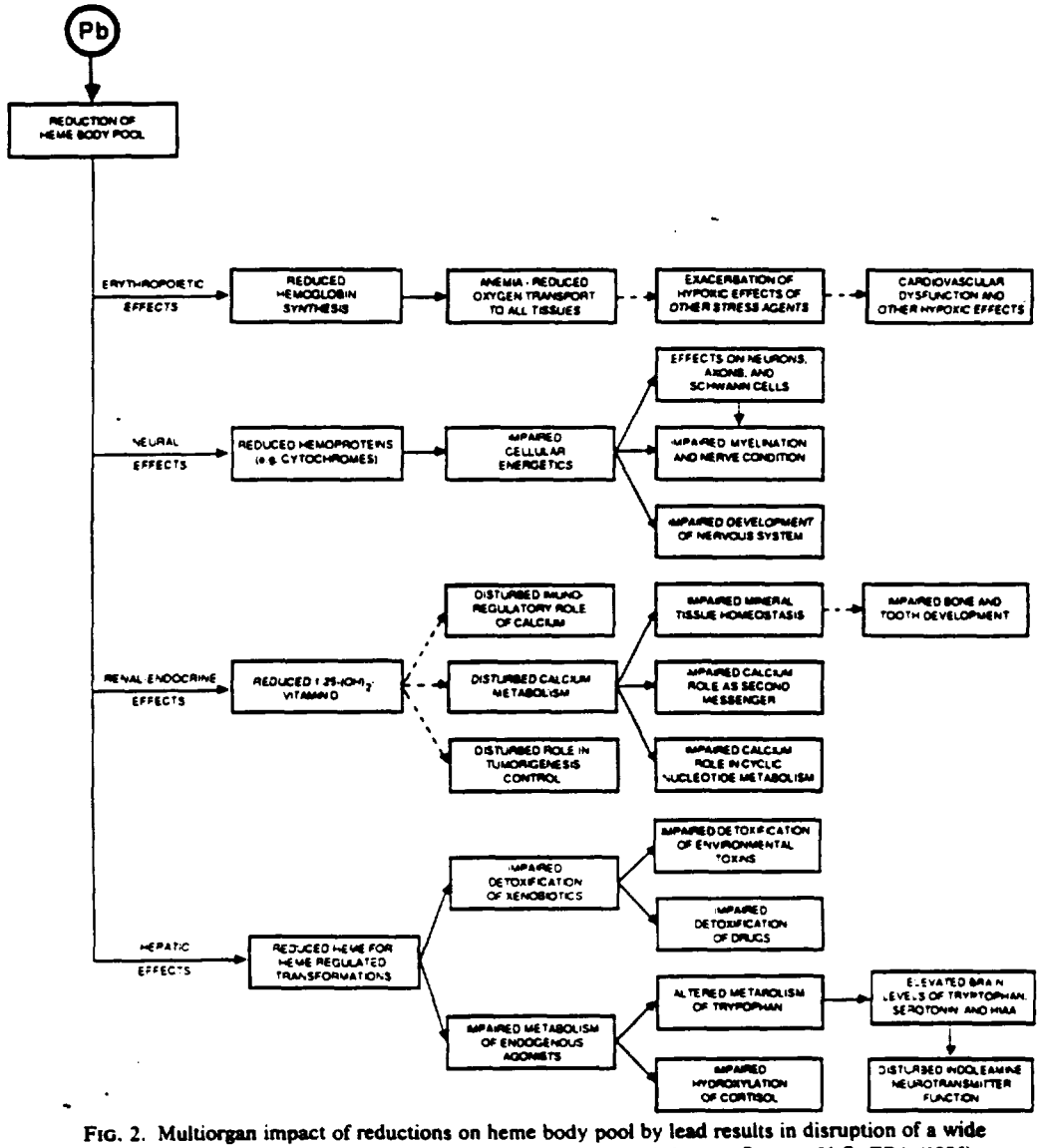

FIG. 2. Multiorgan impact of reductions on heme body pool by lead results in disruption of a wide variety of important physiological processes in many organs and tissues. Source: U.S. EPA (1986).

dent at blood lead levels of 10 to 15 μg/dl, and possibly lower (U.S. EPA, 1986). Some recent work also suggests that auditory acuity is reduced at these levels as well.

At levels still below 20 μg/dl, erythrocyte protoporphyrin is elevated, and disturbances in 1,25-$(OH)_2$-vitamin D and early signs of impaired erythropoietic pyrimidine metabolism are evident. Cross-sectional studies reveal IQ deficits at

TABLE 3
LOWEST OBSERVABLE EFFECT LEVEL (Pb–B) FOR EFFECTS IN CHILDREN[a]

Lowest effect Pb–B (μg/dl)	Neurological effects	Heme synthesis effects	Other effects
10–15 (prenatal and postnatal)	Deficits in neurobehavioral development (Bayley and McCarthy Scales); electrophysiological changes	ALA-D inhibition	Reduced gestational age and weight at birth; reduced size up to age 7–8 years
15–20		EP elevation	Impaired vitamin D metabolism; Py-5'-N inhibition
25	Lower IQ, slower reaction time (studied cross-sectionally)		
30	Slowed nerve conduction velocity		
40		Reduced hemoglobin; elevated CP and ALA-U	
70	Peripheral neuropathies	Frank anemia	
80–100	Encephalopathy		Colic, other GI effects; kidney effects

[a] Adapted from U.S. EPA (1986), with updating.

Pb–B levels starting below 25 μg/dl and at progressively higher levels as well. The clear impression to be gained from Table 3 is that a number of effects are detectable at the Pb–B range of 15–25 μg/dl and even lower.

The Congressional report (U.S. ATSDR, 1988) provides child population lead exposure estimations in various chapters in terms of three Pb–B ceilings: 25 μg/dl (based on CDC, 1985), 20 μg/dl (based on WHO, 1987), and 15 μg/dl (based on U.S. EPA, 1986). Selecting these particular values for the purposes of this report does not imply that lower levels are safe. Comparing the information in Table 3 with stratified estimates of numbers of children at these Pb–B ceilings in Chapter V of the Congressional report gives an indication of the persistence of low-level exposure in the United States.

A detailed dose–response relationship in a population of children has been described only for EP elevation. Using probit techniques, Piomelli *et al.* (1982) have reported the EP dose–response relationship depicted in Fig. 3. This plot represents response at both 1 and 2 standard deviations as Pb–B rises and establishes a threshold for the index effect at ca. 15 μg/dl Pb–B.

D. PERSISTENCE OF ADVERSE HEALTH EFFECTS FROM LEAD EXPOSURE IN YOUNG CHILDREN

For this topic, these questions should be considered:

(1) What is the time frame to be defined under the term persistent? Does it include only childhood or the entire life span?

(2) Are the persistent effects to be compared with societal or clinical values and

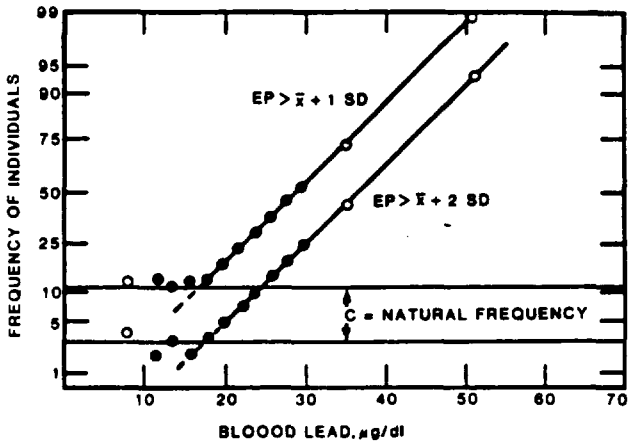

FIG. 3. Dose–response and threshold Pb–B curves for EP increase with an entire population sample using probit analysis. Several groups of Pb–B were used. From the lowest Pb–B group, a "normal" reference EP was calculated to be 21.7 µg/dl. Geometric mean plus 1 SD = 33 µg/dl EP and geometric mean plus 2 SD = 53 µg/dl EP. Intersection of probit regression lines with respective ordinate *C* value occurred at threshold levels of 16.4 and 16.6 µg Pb/dl. Source: Piomelli *et al.*, 1982. Reprinted with permission of the authors and the National Academy of Sciences.

judgments that encompass optimal psychological and physical well-being, or simply the absence of overt disease?

(3) If lead-associated effects induced in childhood resolve themselves beyond childhood, what evidence remains that there are no deficits in overall development associated with these effects? For example, even if IQ decrements are present only in early childhood, what other more permanent deficits may be acquired in terms of emotional development, social interactions, and other facets of human development?

(4) Might one have to reconcile de facto meanings for the inherent reversibility or irreversibility of certain effects? As noted earlier (EPA, 1986), even in the face of biological reversibility there may be socioeconomic irreversibility of lead exposure and hence potential adverse health effects. In addition, there may be persistence of internal lead exposure well beyond early childhood in individuals burdened by bone lead accumulations that are later released into other compartments of the body.

It is generally considered that lead-induced injuries to the central nervous system are largely irreversible (American Academy of Pediatrics, 1987). Table 4 tabulates various lead-induced effects due to prenatal or postnatal exposure, with comments about the persistence of such effects. These assessments spring from both cross-sectional and prospective epidemiologic studies, and provide multiple indications of persistent, long-term health effects in children. However, firm conclusions about the persistence and ultimate impact of such effects are difficult to state at present because of the limited time spans over which children have thus far been studied. A more definitive assessment of the persistence issue will require the continuing examination of children in prospective studies.

TABLE 4
RELATIVE PERSISTENCE OF ADVERSE HEALTH EFFECTS IN INFANTS AND CHILDREN

Adverse effect	Length of study period(s)	Comments
Reduced gestational age and birth weight	Birth onward, developmental deficits. Pregnant mothers enrolled prior to delivery, offspring followed up to 24 months postnatally, thus far.	Major predictors for persisting, later developmental problems.
Deficits in Bayley Mental Development Index	Up to 24 months thus far.	Early neurobehavioral tests assess functional health of nervous system in infants.
Preliminary indications of deficits in McCarthy Scales performance at 5 years of age	Relationship observed over 3-year interval thus far.	Effect related to postnatal exposure at 2 years of age.
IQ deficits in school-age children and other measures	With higher Pb–B levels, IQ deficits persist. Low levels show several years of persistance w/Pb–dentine; may not be detectable with Pb–B. Reaction time effects appear to persist up to 6 years postexposure, using Pb–tooth as index.	Any persistence in IQ deficits carries risk for other psychosocial effects. Good evidence for persistence of cognitive deficits stems from nonhuman primate data showing related but irreversible impairment of learning acquisition. Ongoing prospective studies will provide key to many questions.
Neurophysiological disturbances	Five years after most Pb-vulnerable period, effects remain on CNS sensory pathways depending on conditioning paradigm employed.	Passive conditioning stimulation approaches show persistence up to 2 years; no persistence at 5 years. Active conditioning task testing not done originally.
EP elevations	Elevations persist with both external exposure and endogenous (bone) lead release.	Cascade of effects from body heme pool disturbances include neurological development.

[a] Source: U.S. EPA (1986) and Davis and Svendsgaard (1987), with updating.

As noted by Grant and Davis (1989), ontogeny is characterized both by its plasticity and by its sequential dependency. Developing organisms may be able to compensate for certain deficiencies, if they occur early enough in the maturation of the individual. For example, children often show catch-up growth spurts. Thus, it is possible that early developmental lags, particularly those that are somewhat subtle, could "disappear" at later ages. But it is also important to note that, even if a lead-induced lag in cognitive or physical development were no longer *detectable* later (which depends very much on the sensitivity of available measurement methods), this would not necessarily imply that the earlier impairment was without consequence.

Research in developmental and physiological psychology has clearly shown that the actualization of behavioral capabilities requires appropriate periods of functional neural activity for proper development. Thus, even transient or, in themselves, reversible deficits during early development may have potentially serious and long-lasting sequelae. Moreover, secondary effects of early develop-

mental perturbations need not be strictly sequential. Given the complex interactions that figure into the psychosocial development of children, attempts to compensate for lead-induced deficits in one area of a child's development may affect other areas of development.

Of particular relevance to the question of persistent effects of lead on neurobehavioral function is a large body of experimental animal research that demonstrates deficits in various aspects of behavior for several years after experimentally controlled lead exposure has been terminated. These effects have been reliably and consistently found in nonhuman primates as well as other species. Discussion of these studies is beyond the scope of this report and one can refer to the exhaustive discussion of this aspect in the EPA document (U.S. EPA, 1986).

We have a rather good understanding about the persistence of the effects induced in the heme biosynthesis pathway when exposure is maintained. In populations at high risk for lead exposure, EP elevation is a chronic problem (U.S. EPA, 1986; CDC, 1985). Furthermore, elevation of EP can persist beyond early childhood. Persistence in EP elevation is particularly likely in cases where Pb–B levels remain elevated because of resorbable bone lead. One need only examine Fig. 2 to realize the potential for extended persistence of effects in a myriad of other systems, when the heme pool in the body remains disturbed.

In summary, then, and in response to legislative language in Section 118(f), we can state that various adverse effects of lead do persist, or can potentially persist, over extended periods. Furthermore, such persistence need not be long to have implications for future deleterious effects on physical and psychosocial development.

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